Remarks

Claims 2, and 4-6 where cancelled. The subject matter of claim 2 has been incorporated into independent claim 1.

35 U.S.C. 101 Rejection

Original claims 4-6 were rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. These claims have been cancelled and Applicants respectfully request the rejection be withdrawn.

35 U.S.C. 112, second paragraph rejection

Claims 4-6 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. These claims have been cancelled and Applicants respectfully request the rejection be withdrawn.

35 U.S.C. 103(a) Rejection

Applicants disagree with the rejection of claims 1-9 in light of the Grant et al, and Vrana et al., and further in view of Zimmermann and Pandolfi et al..

The holding in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1390 does not apply to the combinations described in the present application. In KSR, the Supreme Court reminded us that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (Slip Op. at 12).

The combinations described in the present application do not "yield predictable results". The outcome of combining two therapeutic agents is unknown in the field of oncology. The combination of two therapeutic agents may lead to positive results, such as synergism and/or additive effects or, on the other hand, the combination of two therapeutic agents may lead to negative results. Another possibility is that therapeutic agents may be most effective as single agents in the treatment of cancer.

The ordinary skilled artisan would not be able to predict the outcome of combining two therapeutic agents, such as imatinib and an HDAC inhibitor, based on the descriptions in the references cited. None of the references cited by the Examiner provide the necessary motivation for the ordinary skilled artisan to predict the successful therapeutic benefits of combining imatinib with HDAC inhibitors.

The Examples in the specification clearly support Applicants' position that the claimed combination is unobvious in light of the prior art. The testing of imatinib and SAHA by the Applicants on various cell lines, including K562 and LAMA 84 cell lines show the synergist therapeutic effect of the combination of Imatinib and the HDAC inhibitors. The synergism found by combining imatinib with SAHA is unpredictable to a skilled artisan. Furthermore, the testing of imatinib and sodium butyrate by the Applicants on various cell lines show the synergist

therapeutic effect of the combination of Imatinib and the HDAC inhibitors. The synergism found by combining imatinib with sodium butyrate is unpredictable to a skilled artisan.

The Examples should not be construed narrowly. The synergistic effects of the claimed combination is an example of how imatinib will react with the class of compounds that are HDAC inhibitors. Therefore, the Examples also support the HDAC inhibitors recited in the claims of the present application.

Synergistic Effects of imatinib and SAHA

Table 1A illustrates a clear increase in apoptosis when imatinib in concentrations of 100nM and 250nM is combined with 2.0μM of SAHA. The large majority of cells, i.e. ~75% are apoptotic when K562 cells are treated with 250nM of imatinib in combination with 2μM of SAHA, please refer to page 17 of the specification. Table 1B describes when cells are exposed for 24 hours to 250nM of imatinib in combination with increasing concentrations of SAHA. A shape increase in apoptosis is noted at 1.0μM SAHA and, at SAHA concentration of 1.5μM, the majority of cells are apoptotic, please refer to page 18 of the specification.

The synergistic results described in Table 1C is considered unpredictable because it does not necessarily follow that combining two therapeutic agents would result in synergism. The Combination Index (CI) values were lower than 1.0, which illustrates to a skilled artisan that imatinib and SAHA produce a synergistic reaction.

Additional studies on this combination, including but not limited to, time course studies, clonogenic assays, monitoring of hemoglobin, were conducted by Applicants to further investigate this combination.

The time course studies of K652 cells exposed to 250nM imatinib with/without 2.0 μM SAHA showed that after 48 hours of combined treatment, over 90% of cells are apoptotic, please refer to table 2A on page 19 of the specification. Similar results were observed when loss of mitochondrial membrane potential is monitored. The clonogenic assays were performed to determine whether potentiation of apoptosis in K562 cells treating with imatinib in conjunction with an HDAC inhibitor would be associated with loss of leukemic cell self-renewal capacity. The combined treatment of SAHA and Imatinib resulted in greater than a 2-log reduction in colony formation, please refer to Table 2C. Hemoglobin (Hgb) production was monitored in K562 cells treated with SAHA ± Imatinib and the findings indicate that co-treatment of Bcr/Abl K562 cells with imatinib and SAHA does not promote differentiation, but instead suggests that the extensive apoptosis that occurs under these conditions instead prevents this process, please refer to page 21 of the specification.

The Examples described above illustrate the need for skilled artisans to conduct multiple tests of the combination to determine its therapeutic effectiveness as a combination therapy.

Similar tests were conducted using the combination of imatinib and SAHA on LAMA 84 cells. The majority of LAMA 84 cells exposed to 1.0μM SAHA in combination with Imatinib became apoptotic, please refer to Table 4 on page 24 of the specification.

Consistent with the results obtained in K562 cells, treatment of LAMA 84 cells with the combination of imatinib and SAHA resulted in down regulation of Raf, $p21^{CIP1}$, cyclin, D_1, Mcl-1, phosphor-STAT5, enhanced underphosphorylation and cleavage of pRb, and a dramatic increase in JNK phosphorylation.

Synergistic Effects of imatinib and sodium butyrate

K562 and LAMA 84 cells are exposed to concentrations of imatinib and sodium butyrate and co-administration resulted in a marked increase in apoptosis in both cell lines, please refer to the Table on page 25 of the present application. The synergistic results described in Table on page 25 are considered unpredictable because it does not necessarily follow that combining two therapeutic agents would result in synergism.

The Cited Prior Art References Do Not Teach or Suggest the Claimed Invention

As stated above, none of the references cited by the Examiner provide the necessary motivation for the ordinary skilled artisan to predict the successful therapeutic benefits of combining imatinib with HDAC inhibitors.

The Examiner argues that Grant et al. teaches the rational for combining imatinib with a HDAC inhibitor where the HDAC inhibitor is SAHA. The standard for determining obviousness is not based on rational. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The Examiner refers to the following statement in Grant et al. on page 4 of the Official Action dated September 5, 2007:

> Grant teaches that "chemotherapeutic regimens would be most effective when they employed agents that (i) exhibited different mechanisms of action; (ii) had non overlapping toxicities; (iii) could be given at or near the maximally tolerated dose and (iv) were individually effective against the disease in question"

The passage above does not provide guidance for a skilled artisan to make the claimed invention. According to the Examiner, imatinib and SAHA are ideal candidates for combination therapy. Again, the Examiner is reminded that the test for obvious is based on the three criteria stated above. Without the teaching or suggestion, one of ordinary skill in the art would not have been motivated to combined imatinib and SAHA.

The holding in KSR International Co. v. Teleflex Inc., 82 USPQ2d 1385, 1390, should not apply to the present invention because the present invention relates to a different field of science. The patentable subject matter described in KSR related to an invention in the mechanical arts. Anticipated success in the pharmaceutical arts is difficult to ascertain. The success of one therapeutic agent would not give "good reason" for a person of ordinary skill in the art to pursue other known options, such as combining that agent with another agent. Combining two therapeutic agents for the treatment of a specific disease requires experimentation. As the Examples illustrate, the claimed combination exhibits synergist effects in therapy. Grant et al. does not teach or suggest the claimed combination or the synergistic effects associated with the claimed combination. Therefore, the present application is nonobvious over Grant et al.

Carroll et al. and Vrana et al. also do not teach or suggest the claimed combination. Without the specific motivation, a person of ordinary skill in the art would not look to the prior art references and arrive at the claimed invention. A skilled artisan would not have been motivated based on the teaching of one therapeutic agent to combine this agent with another to arrive at the claimed invention.

Zimmerman and Padnolfi et al. also fail to provide the requisite motivation. As in the case with Carroll et al. and Vrana et al., Zimmerman and Padnolfi et al. each describe the agents separately. Although Zimmerman and Padnolfi et al. are cited for the their description of treating cancer, neither reference describes a motivation to combine these agents or the success as described in the Examples of the present invention.

The claimed invention is non-obvious over the cited references because the references to do not teach or suggest or provide the requisite motivation for a person of ordinary skill in the art to make the claimed invention. Applicants respectfully request the obviousness rejection be withdrawn from consideration. Entry of this Response is respectfully requested.

Respectfully submitted,

Oona Manzari

Oona A. Manzari
Attorney for Applicants
Reg. No. 48,152
Phone No. (862) 778-7852

Novartis
Corporate Intellectual Property
One Health Plaza, Building 104
East Hanover, NJ 07936-1080

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